

R E M A R K S

Claims 1-19 are pending. No new matter has been added by way of the present amendment. For example, new claim 19 is supported by the present specification at, for example, page 7, line 15, page 4, line 32 and page 13, line 28. Accordingly, no new matter has been added.

In view of the following remarks Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

Applicants note that the Request for Continued Examination also included a request that the amendment submitted on August 19, 2002 be entered on the record. Thus, pursuant to the Examiner's Advisory Action dated September 4, 2002 the entry of these amendments has overcome the rejection of claims 9 and 10 under 35 U.S.C. §112, second paragraph and the objection to the specification referring to trademarks. Accordingly, the only outstanding issue from the May 17, 2002 Office Action is the rejection under 35 U.S.C. §103(a).

Issues Under 35 U.S.C. §103(a)

Claims 1-18 stand rejected under 35 U.S.C. §103(a) as being obvious over Georgiades '683 in view of Manabe '315. Applicants respectfully traverse this rejection.

Georgiades '683 discloses the addition of a detergent as a

means of virus inactivation. Additionally, Georgiades discloses that membrane filtration is a means of virus removal. Manabe '315 discloses virus removal by membrane filtration.

The presently claimed subject matter relates to a method wherein a purified biologically active protein is subjected to a non-ionic detergent and then later subjected to filtration on a virus removal filter. This combined set of steps is neither suggested nor disclosed by the cited references. According to the present invention, when non-ionic detergents are used instead of albumin (utilized by the prior art), for the stabilization of purified protein solutions, virus filtration can be performed with superior filter performance while maintaining efficient virus removal. However, it is important to distinguish the use of detergents according to the present invention in comparison to the prior art.

According to the present invention detergents and filtration are not directed to the same end. Rather, detergents do not have a primary role in virus removal, rather, they unexpectedly render the filtration of biologically active proteins through virus removal filters much more efficient. That is, addition of detergents to the solution prior to virus removal filtration prevents filter clogging and improves protein recovery. Neither Georgiades '683 nor Manabe '315 suggests or disclose that detergents are able to prevent protein losses or clogging of the filter. Applicants have previously provided an analysis of the

factors involved in the present process. However, the Examiner has indicated that the provided results are not sufficient to support a holding of unexpected benefits. Further, the Examiner asserts that the comparison shows 12-14% differences in recovery when detergent is compared to albumin. The Examiner asserts that this difference is within normal biochemical error and that no statistical analysis has been provided to indicate otherwise. Applicants respectfully traverse. In the Declaration pursuant to 37 C.F.R. §1.132 attached hereto, Applicants have provided a statistical analysis which definitively concludes that the presently claimed subject achieves unexpectedly superior results.

A review of the Declaration reveals that the difference in recovery between detergent compared to albumin was statistically significantly higher in the presence of detergents rather than albumin. In Table 1 of the present application only one pair of experiments was carried out. However, when all experiments carried out are analyzed, protein recovery was significantly higher in the presence of detergent than in the presence of albumin ($p < 0.05$, t test). This data has been presented in the attached Declaration.

In the prior art, albumin has been typically added to pure solutions of biologically active proteins to prevent losses of a biologically active protein. However, the present claimed subject matter demonstrates that detergents are statistically more effective than albumin in the prevention of protein loss during

virus removal filtration.

Improvement of protein recovery by 12-14% is very important in terms of industrial exploitation of the present application. In the production of interferons, a typical batch size is one gram of protein corresponding to 200,000 Mill IU. An improvement of the yield with 10% means 20,000 Mill IU interferon, which costs about \$200,000 US. Additionally, the flux through the filter was statistically faster at the end of filtration in the presence of detergents compared to albumin ($p < 0.05$, t test). This data is also shown in the attached Table. In fact, several times more interferon-containing solution could be filtered with the same filter membrane area in the presence of detergents compared to albumin. This is significant since virus removal filters are very costly (1 m² Planova 15 N cartridge costs \$4,000 US) and can only be used once. Accordingly, industrial exploitation in the present application provides considerable benefits.

In summary, the prior art cited by the Examiner fails to suggest or disclose the presently claimed subject matter. Moreover, even if, *arguendo*, the Examiner has hypothetically established a *prima facie* case of obviousness, the prior art fails to recognize the unexpected superior benefits according to the present invention. That is, when a presently claimed subject matter is carried out, the use of detergents prevents clogging of the membrane when protein-containing solutions are filtered through a virus removal filter, thus increasing the yield the

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protein recovery and increasing the life of the filter. These results are unexpected in view of the prior art, thus, any hypothetical *prima facie* case of obviousness is moot. Reconsideration and withdrawal of this rejection is respectfully requested.


If the Examiner has any questions or comments, please contact Craig A. McRobbie, Registration No. 42,874 at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Respectfully submitted,

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By

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Attachment: Version with Markings to Show Changes Made

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 19 has been added